Prevalence of anxiety and depression in pulmonary hypertension and changes during therapy

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Abstract: BACKGROUND: Pulmonary hypertension (PH) leads to reduced health-related quality of life (HRQoL). OBJECTIVE: To investigate the prevalence and course of anxiety and depression and their association with HRQoL, disease severity and survival in PH. METHODS: 131 PH patients (91 pulmonary arterial, 30 chronic thromboembolic, 10 due to lung disease; 84 female, 47 male) had repeated assessments with the Hospital Anxiety and Depression Scale (HADS), HRQoL, six-minute walk distance and WHO functional class during a mean course of 16 ± 12 months. RESULTS: Among the 49 incident and 82 prevalent PH patients, the HADS score was positive in 53%/21% (depression), 51%/24% (anxiety) and 63%/26% (total score) (all $p < 0.05$). The HADS score was improved at the second assessment in incident patients. The HADS score correlated with HRQoL at all consecutive assessments and with functional class until the third assessment, but not with baseline hemodynamics, age or gender. CONCLUSION: Mood disorders remain underdiagnosed in PH. The higher prevalence of anxiety/depression in incident versus prevalent patients and the improvement over time may indicate an amelioration of mood disorders after PH diagnosis and treatment.

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Prevalence of Anxiety and Depression in Pulmonary Hypertension and Changes during Therapy

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Key Words
Pulmonary hypertension · Pulmonary arterial hypertension · Chronic thromboembolic pulmonary hypertension · Anxiety and depression · Health-related quality of life

Abstract
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Introduction

Pulmonary hypertension (PH) represents a group of rare disorders with a progressive course and a dismal prognosis if untreated [1]. In the absence of relevant heart and lung diseases, the two major forms are pulmonary arterial hypertension (PAH) and chronic thromboembolic PH (CTEPH). The majority of patients with CTEPH can be substantially improved or cured by surgical pulmonary endarterectomy [2, 3]. Since the availability of novel disease-targeted medical therapies, the prognoses for PAH and inoperable CTEPH have improved; however, these chronic disorders still cannot be cured. PH due to left heart disease and PH due to hypoxia/lung disease remain difficult to treat. PH-targeted treatment has so far

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not been found to improve symptoms nor to reduce morbidity/mortality in these groups [4, 5].

Due to unspecific initial symptoms, PAH diagnosis is usually delayed from the onset of symptoms between 1.5 and 4 years [6, 7]. This prolonged duration to diagnosis can lead to anxiety, depression and stress. After diagnosis the emotional burden persists along with initiation of complex therapies and potentially progressive physical impairment. Furthermore, patients often appear healthy at rest and thus might not be taken seriously by health care providers or their environment in their constrained daily life [8]. Anxiety and depression are highly prevalent in chronic diseases and have also been commonly found in prevalent PAH patients under chronic therapy [9–16].

In rare diseases, such as PAH or CTEPH, registries provide valuable information on the baseline characteristics and outcomes of the disease [17]. We have built a PH database in our daily practice, which includes classification according to international guidelines [18], and have prospectively collected data according to standardized procedures, which allows long-term observation. In this database, we have also included several instruments for assessing health-related quality of life (HRQoL) and emotional disorders by the Hospital Anxiety and Depression Scale (HADS) [17].

In the REVEAL registry, a multicenter observational PAH cohort, 25% of patients reported symptoms of depression, but these symptoms were not systematically assessed by the questionnaire [15]. Studies which conducted screening for depression with standardized instruments, mainly self-administered questionnaires, found a prevalence ranging from 10 to 55% [9–14].

The aim of the present study was to evaluate the prevalence of anxiety and depression in incident and hitherto untreated as well as in prevalent and pretreated patients with a diagnosis of mainly PAH or inoperable CTEPH, and to look for a correlation of the mood disorders with markers of disease severity, such as pulmonary hemodynamics, exercise capacity and quality of life. Repeated assessments of depression and anxiety after initiation of or during disease-targeted therapy were performed to study the course of these mood disorders and their correlation with symptoms.

Methods

Study Subjects

All patients with PAH, CTEPH or other types of PH seen and diagnosed at our clinic gave their written informed consent to have their data registered [17]. The local database of the PH center at the University Hospital of Zurich was reviewed for patients with PH who had filled in HADS questionnaires. Starting in 2012, this questionnaire has been handed to every PH patient at 0, 3, 6, 12 and 24 months (newly diagnosed) or at every annual visit (treated). Precapillary PH was diagnosed by a mean pulmonary arterial pressure ≥25 mm Hg, with a pulmonary artery wedge pressure ≤15 mm Hg during right heart catheterization, and classification was made according to international guidelines, with all patients having ventilation-perfusion scan, pulmonary function test, rheumatologic assessment, thoracic angio-CT and/or pulmonary angiography [1]. Incident patients were defined as patients who had filled in the HADS at the time of the diagnostic right heart catheterization and were not yet receiving targeted therapy; the remaining patients were categorized as prevalent. The study was approved by the Zurich cantonal ethical review board (KEK 2014-0592).

Demographics, Exercise Performance, Anxiety and Depression Score and Quality of Life

During the initial diagnostic right heart catheterization, mean pulmonary arterial pressure, pulmonary vascular resistance, cardiac index, as well as arterial and mixed venous oxygen saturation were noted. At the same time the patient's demographics (age, sex, height, weight and calculated body mass index), medical history, WHO functional class and six-minute walk distance (6MWD) were assessed according to standard protocols. Between 2012 and 2014, patients' anxiety and depression was measured using the HADS questionnaire [19]. The HADS is a fourteen-item questionnaire from which an anxiety and depression subscale can be derived. Subscore values >5 points correspond to increased anxiety and/or depression, a total score >9 is pathological [20]. It is considered a powerful tool for screening for symptoms of depression and anxiety, but has only rarely been used in PH [21]. We used cut-offs that have recently been validated with regards to sensitivity and specificity in chronically ill COPD patients [20].

HRQoL was assessed by the Minnesota Living with Heart Failure (MLHF) questionnaire (equaling the Living with Pulmonary Hypertension questionnaire). The MLHF questionnaire consists of a general score (range 0–105), a physical subscore (range 0–40) and an emotional subscore (range 0–25), with higher scores reflecting poorer quality of life. In addition, we used the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) questionnaire specifically designed for PH, consisting of scales for symptoms (25 items), activity limitation (15 items) and quality of life (25 items), with a maximum score of 65 and likewise higher scores reflecting worse HRQoL [22–24].

Statistical Analysis

Results are expressed as median (interquartile range) or mean ± standard deviation according to non-normal or normal distribution (tested by the Kolmogorov-Smirnov test). The non-parametric Mann-Whitney U test was used to compare two independent samples; differences in the course of the disease were calculated using the Wilcoxon test. Fisher's exact test was used to compare frequencies of mood disorders in incident and prevalent patients. Survival was estimated using the Kaplan-Meier method with the Breslow test (generalized Wilcoxon). Factorial analysis was used to build a composite factor of the various related HRQoL parameters and the three HADS parameters. A p value <0.05 was considered statistically significant.

Table 1. Patients' baseline characteristics

Patients' characteristics	n (%) or median (IQR)	Incident patients	Prevalent patients
Total number of patients	131 (100%)	49 (37%)	82 (63%)
Females/males	84/47 (64%/36%)		
Age, years	67 (51–75)	67 (47–76)	67 (55–74)
Body mass index	25 (21.5–28.0)	26 (23.0–30.0)	25 (21.0–27.0)
PH classification			
PAH	91 (70%)	38 (78%)	53 (65%)
Idiopathic	72 (55%)	29 (59%)	43 (52%)
Associated with connective tissue disease	10 (8%)	5 (10%)	5 (6%)
Associated with portal hypertension	4 (3%)	3 (6%)	1 (1%)
Associated with HIV infection	1 (1%)	0 (0%)	1 (1%)
Associated with congenital heart disease	4 (3%)	1 (2%)	3 (4%)
Severe PH due to lung diseases	10 (8%)	4 (8%)	6 (7%)
CTEPH	30 (23%)	7 (14%)	23 (28%)
Baseline hemodynamics			
Heart rate, bpm	78 (69–89)	79 (72–87)	77 (69–90)
Mean pulmonary artery pressure, mm Hg	40 (32–51)	35.5 (28–49)	42 (34–54)*
Cardiac index, liters/min/m^2	2.8 (2.3–3.4)	3 (2.0–3.7)	2.7 (2.0–3.2)**
Right atrial pressure, mm Hg	8 (5–10)	8 (6–12)	8 (5–10)
Wedge pressure, mm Hg	12 (9–14)	12 (10–14)	12 (8–14)
Arterial oxygen saturation, %	92 (88–95)	91 (88–95)	92 (88–95)
Mixed venous oxygen saturation, %	65 (60–72)	63 (60–72)	67 (60–72)

HIV = Human immunodeficiency virus; IQR = interquartile range.
* $p < 0.05$; ** $p < 0.01$.

Results

Baseline Characteristics

A total of 131 patients were included. Most of the patients (66%) were diagnosed with PAH, the second largest group (23%) consisted of CTEPH patients (inoperable or persistent after pulmonary endarterectomy). We also included small groups with severe PH due to lung disease or multifactorial origin.

The patients' characteristics at the time of PH diagnosis are shown in table 1, which consisted with the time of the first HADS in 37% of patients (incident group). 63% of patients had received PAH-targeted medical treatment for a mean time of 36 (15–74) months before the screening test for depression and anxiety was performed (prevalent group). At the time of analysis, these prevalent patients were treated with the following PAH-targeted therapies: endothelin receptor antagonist (60%), phosphodiesterase type 5 inhibitor (44%), soluble guanylate cyclase stimulator (8%), or prostanoids (21%); 36% were on combination therapy and 13% with CTEPH underwent pulmonary endarterectomy.

Most of the patients were in WHO functional class III (43%) at the time of first HADS screening and had a median 6MWD of 480 m (375–545) at a mean age of 67 years (51–75).

Quality of life measured by the MLHF questionnaire and the CAMPHOR questionnaire was reduced (corresponding to high scores; table 2), but better (corresponding to lower scores) in prevalent patients under therapy compared to incident patients.

Prevalence of Depression and Anxiety

Overall, the median HADS score for depression was 3 (2–7) and that for anxiety was 4 (2–7); the total score was 7 (4–14). In 46% of patients either anxiety, depression or total scores were elevated, revealing symptoms consistent with a diagnosis of depression or anxiety mood disorder. More than one third of patients had elevated subscores (>5), and 40% had a total HADS score >9. During initial questionnaire screening, incident patients had higher HRQoL and HADS scores, meaning that they perceived their HRQoL and their mental health as worse than the group of prevalent patients.

Table 2. Baseline assessment of symptoms, walk distance, non-invasive hemodynamics, anxiety, depression and quality of life in incident and prevalent PH patients

	n (%) or median (IQR)		
	all patients (n = 131)	incident patients (n = 49)	prevalent patients (n = 82)
WHO functional class	3 (2–3)	3 (2–3)	2 (2–3)**
I/II	58 (44.2%)	13 (26.5%)	45 (54.9%)
III	56 (42.7%)	26 (53.1%)	30 (36.6%)
IV	15 (11.5%)	10 (20.4%)	5 (6.1%)
6MWD, m	480 (375–545)	435 (311–509)	484 (412–552)*
SpO_2 after 6MWD, %	90 (84–94)	90 (85–95)	90 (82–94)
Tricuspid pressure gradient (echo), mm Hg	59 (39–79)	62 (46–78)	50 (31–83)
LHFQ general, points	27 (13–47)	43 (24–57)	21 (10–38)**
LHFQ physical, points	15 (8–22)	21 (12–26)	13 (6–20)**
LHFQ emotional, points	4 (1–11)	10 (5–17)	3 (0–8)**
CAMPHOR activity, points	7 (3–12)	11 (7–15)	5 (2–9)**
CAMPHOR symptoms, points	6 (3–10)	8 (5–11)	5 (2–9)*
CAMPHOR quality of life, points	3 (1–7)	6 (2–12)	1 (0–5)**
HADS screening started, months after baseline	11 (0–46)	0 (0–1)	36 (15–74)**
HADS depression, points	3 (2–7)	6 (3–9)	3 (1–5)**
HADS anxiety, points	4 (2–7)	6 (3–9)	3 (2–5)**
HADS total, points	7 (4–14)	11 (7–17)	6 (3–10)**
Patients with HADS depression >5	43 (33%)	26 (53%)	17 (21%)#
Patients with HADS anxiety >5	45 (34%)	25 (51%)	20 (24%)#
Patients with HADS total >9	52 (40%)	31 (63%)	21 (26%)#

All values account for the time of the first HADS assessment.

IQR = Interquartile range; LHFQ = Living with Heart Failure Questionnaire; SpO_2 = peripheral oxygen saturation.

* $p < 0.05$; ** $p < 0.01$; # Fisher's exact test < 0.01.

Pre-Diagnosed Mood Disorders

15.3% of our patients (n = 20) had previously been diagnosed with and treated for anxiety or depression at the time of the first questionnaire screening. These patients had a median of 7 (3–9) in the anxiety, 8 (3–9) in the depression and 15 (7–18) in the total score. Patients without mood disorders revealed median scores of 3 (2–6) in anxiety, 3 (2–6) in depression and 7 (4–11) in total score. Of the patients who were found to be depressed and/or anxious according to HADS (n = 60, 46%), 23% (n = 14) were under treatment, meaning that >75% were not on antidepressant/anxiolytic therapy. In the collective of patients with mental disorders diagnosed by HADS, patients with pre-diagnosed mental comorbidities had worse HADS scores, indicating insufficient therapy.

HADS Time Course

Eighty patients (61%; 33 incident, 47 prevalent) had filled in the HADS at least twice. Patients who had been screened as depressed/anxious in their first HADS demonstrated two troughs in their HADS score time course, with an initial improvement of mental symptoms followed by a transient slight worsening and late improvement with prolonged follow-up (fig. 1). The first improvement of the total score was significant in incident and prevalent patients, the improved depression subscore was only significant in the incident group (from 8.0 ± 3.5 to 5.0 ± 4.0, p = 0.001), whereas the improved anxiety score was only significant in the prevalent group (from 7.5 ± 3.5 to 6.5 ± 5.0, p = 0.021). Patients who had normal HADS scores at the beginning remained stable or even improved during follow-up. Prevalent patients had a trend towards worsening of symptoms at the end of our observation time. Between the second and the third HADS assessment, the worsening of total HADS score was significant in prevalent patients.

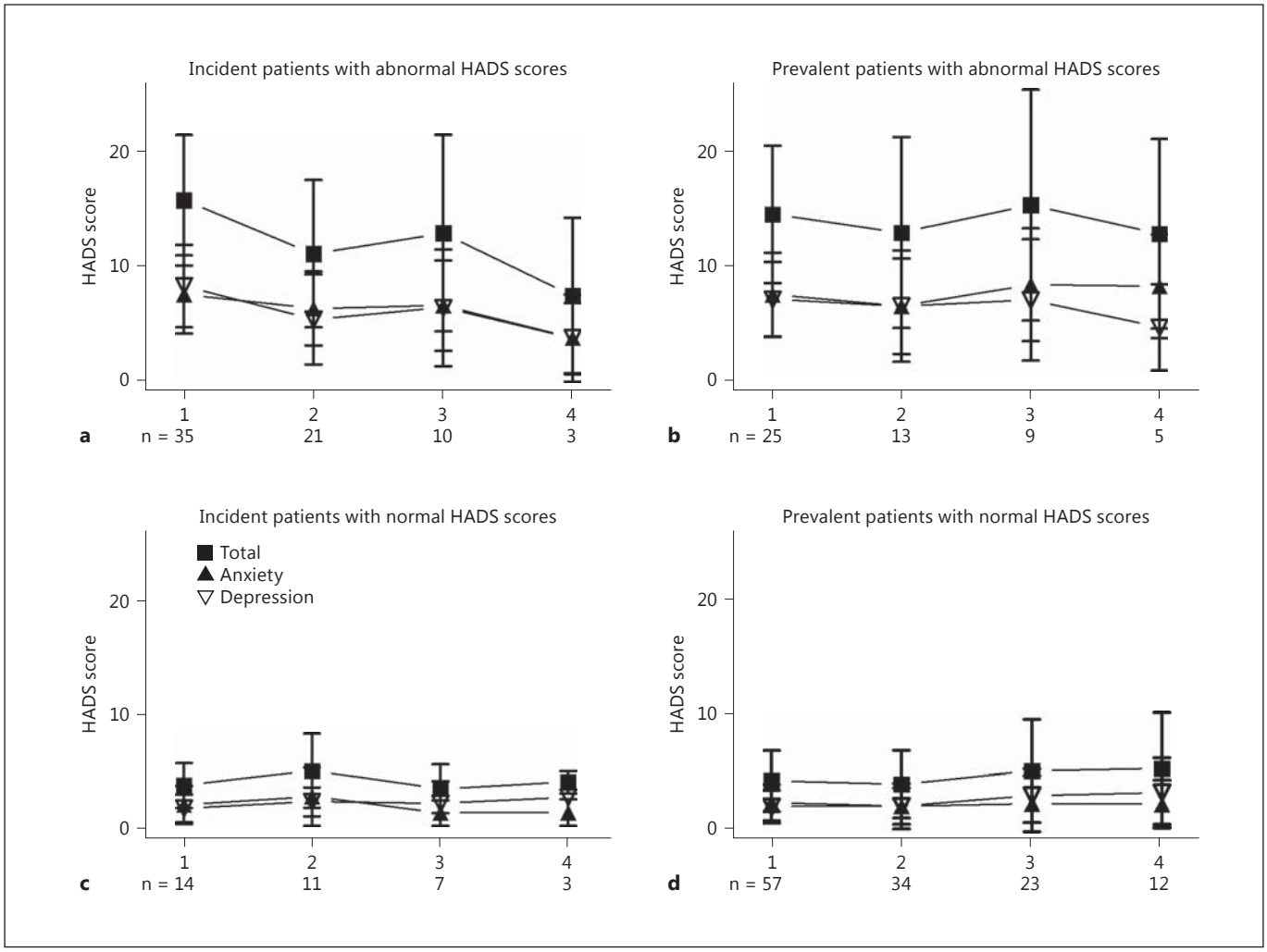

Fig. 1. a Incident patients with abnormal HADS scores. **b** Prevalent patients with abnormal HADS scores. **c** Incident patients with normal HADS scores. **d** Prevalent patients with normal HADS scores. Abnormal: subscore (anxiety, depression) >5, total >9. Time 1: baseline; time 2: 3 months; time 3: 6 months; time 4: 12 months. Significant improvement [6 (4–10) months after filling in the first questionnaire] of the total HADS score in prevalent and incident patients with precapillary PH is seen, as well as improvement of the anxiety subscore in prevalent patients (from 7.5 ± 3.5 to 6.5 ± 5.0, p = 0.021) and of the depression subscore in incident patients (from 8.0 ± 3.5 to 5.0 ± 4.0, p = 0.001) from the first to the second HADS assessment.

Correlation and Regression Analysis

HADS correlated well with HRQoL overall consecutive assessment and with WHO functional class until the third assessment (table 3). However, HADS did not correlate with the 6MWD or other parameters such as age, body mass index or hemodynamics. HRQoL correlated with the 6MWD until the third consecutive questionnaire assessment (table 3).

Transplant-Free Survival

There was no difference in overall transplant-free survival between prevalent and incident patients. However, depressed patients (according to the first HADS depression subscore) had worse overall survival than non-depressed patients with a Breslow value of 0.006 (fig. 2).

Discussion

The results of our study indicate that over one third of PH patients suffer from depression and/or anxiety, with a higher prevalence in incident compared to prevalent patients. Together with the improvement over time, our data may indicate that PH diagnosis, initiation of treat-

Table 3. Correlation coefficients of HADS and HRQoL scores

	6MWD (n = 128)	HRQoL (n = 128)	WHO functional class (n = 129)		6MWD
HADS1 (n = 131)	–0.145	0.763**	0.414**	HRQoL1	–0.383**
HADS2 (n = 80)	0.048	0.738**	0.296**	HRQoL2	–0.273*
HADS3 (n = 49)	–0.041	0.801**	0.39**	HRQoL3	–0.297*
HADS4 (n = 23)	–0.21	0.74**	0.261	HRQoL4	–0.39

All measurements correspond to the time of HADS1/2/3/4.
* $p < 0.05$; ** $p < 0.01$.

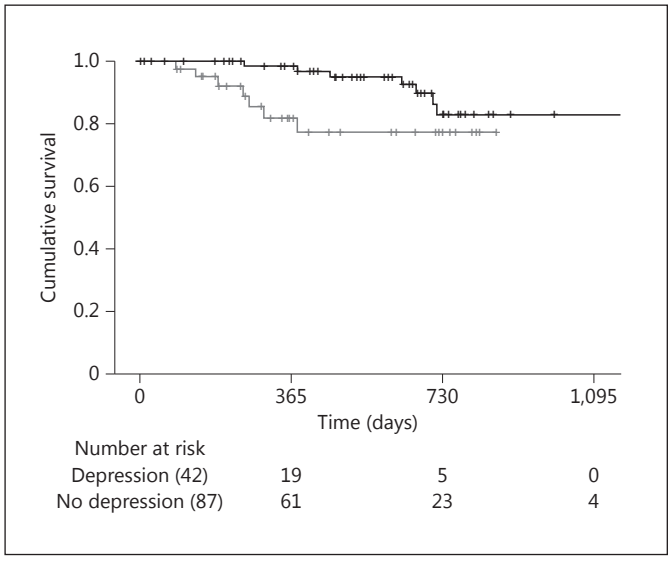

Fig. 2. Kaplan-Maier curve of the survival of depressed (HADS depression >5) versus non-depressed patients.

ment and regular follow-up at a PH center can improve patients' mental symptoms, along with an increased quality of life. Anxiety and depression correlate with WHO functional class and HRQoL, and depressed patients have a worse outcome.

Several studies have shown that depression and anxiety are frequently reported symptoms in PH [9–12, 14], and thus screening for mental disorders has been recommended [25, 26].

The prevalence of depression in studies performed in either PH or PAH patients with self-administered questionnaires varies from 10 to 55%, with the majority ranging around 35%. Anxiety prevalence ranges from 9 to 21% of patients [10, 12, 21]. However, one of those studies used higher score cut-offs than the ones we employed and thus possibly missed some anxious patients.

Although the overall medians of the anxiety and depression subscores and the total HADS score were not elevated compared to the general population [27, 28], we found elevated HADS scores in 46% of patients overall, with a significantly higher percentage of mood disorders in incident versus prevalent patients. Overall, less than one fourth of patients with mood disorders according to HADS were treated for their depression or anxiety. These data point towards underestimation of mental symptoms by health care providers. A recent study found a normative value for anxiety of 6 (4–9) for women and 5 (2–8) for men as well as a depression score of 3 (1–6) for both men and women [27]. In another study in a healthy German population, 21 and 23% had elevated anxiety and depression scores, respectively, although the authors used a higher cut-off of ≥8 and did not look at the total score [28]. In a previous study which used the Depression Anxiety Stress Scale (DASS), it was found that 22% of PAH patients had abnormal scores and were receiving psychopharmacological treatment [13]; thus, this study found a frequency of mood disorders in PAH which was comparable to that of the normal population. Other studies report varying results from 8 to 32% of treated mentally disordered patients with the use of different types of questionnaires [9–11]. In our study, patients previously diagnosed and treated for mood disorders had worse HADS scores than patients without psychopharmacological treatment. This indicates that their mood disorder is undertreated, an unsatisfactory fact that has been previously described in PH [10–12].

Both incident and prevalent patients revealed an improvement in total HADS score from the first to the second assessment, albeit this was more pronounced in incident patients. The reason for this improvement might be multifactorial; the mere handling out of questionnaires, the initiation or change in supportive care or medical therapy, the natural course of mood disorders, or other patient- or environment-related factors might have played a role.

HRQoL and HADS scores assessed in prevalent patients during the course of the disease revealed better scores but worse resting hemodynamics at initial invasive diagnosis than in incident patients. A potential explanation for the worse hemodynamics in prevalent patients might be that PH was diagnosed at a later stage in earlier years. The finding that HADS and HRQoL scores were better and the frequency of mood disorders significantly less in prevalent compared to incident patients points towards a positive effect of treatment and/or follow-up in a specialist center. Incident patients had improved scores 3–6 months after initiation of medical treatment. Thus, this is the first report on a favorable course of mental disorders under supportive care and PAH-targeted medical therapy. An additional reason for the improvement in mood might also be the fact that patients were relieved as they finally got diagnosed with the disease after a sometimes long duration of symptoms and uncertainty. PH is a disease that usually has a long latency period, with a high level of suffering before the diagnosis is definite [6]. Patients may have also adapted to coping strategies with the disease after confirmation of the diagnosis. Care at a specialist PH center with expert physician and nurse counselling and access to patients peer groups might also help to improve patients' mood. The differential impact of drug therapy, health provider support or patients' own coping strategies cannot be defined according to our study, but would be helpful and important to know for health care providers in order to offer the best strategy to support their patients in achieving not only better functional capacity and exercise performance, but also less mood disorders. Our data support a transient improvement of mental disorders by modern PH treatment along with improvements in functional class and HRQoL [29–32]. In an ethnographic study by Kingman et al. published in 2014 [33], PH patients were divided into solution seekers and disease-dominated. Comparing these two strategies shows that a patient can better cope if he is a solution seeker. With patient education, knowledge about the disease and group support, a disease-dominated patient could maybe turn into a solution seeker.

The findings of a worse survival in patients with elevated depression scores and the sustainably elevated HADS scores indicate the need for psychiatric and/or psychological support and counselling for PH patients, potentially along with psychiatric drug therapy in order to improve mental symptoms in this collective. PH clinics often try to establish such support, and psychological support is recommended in the current PH guidelines with an evidence level of 1c [34]. However, financial restraints might limit adequate support for mental disorders. The finding that patients who are depressed according to HADS have a worse survival is remarkable and the reason for this finding is not clear. It might well be that patients with worse functional parameters and hemodynamics tend to be more depressed. We found that an increased HADS score correlated with worse HRQoL, one of the most relevant outcome parameters. However, HADS scores were not correlated with the 6MWD, despite a good correlation of HRQoL with the 6MWD. This may indicate that only measuring HRQoL and 6MWD might not be enough to evaluate patients' mental health: some patients might be depressed or anxious despite a preserved 6MWD – usually more active people who are subjectively seriously limited despite an objectively measured walk distance within the suggested therapeutic goals [34]. However, the different characters and coping strategies of patients might also play a remarkable role.

The limitations of our study are the decreasing number of patients during follow-up and the fact that neither the incident nor the prevalent patient groups are homogeneous, as patients present with different disease stages and have different disease courses at diagnosis and during follow-up. We do not know either for how long patients with pre-diagnosed mood disorders had been treated for their anxiety or depression and whether this time period would have correlated with their diagnosis of PH.

In conclusion, psychological morbidity remains underdiagnosed in precapillary PH. Almost half of patients suffer from depression and/or anxiety, for which only 23% are treated. The slightly lower prevalence of mood disorders in prevalent compared to incident patients might point towards a favorable effect of supportive and PAH-targeted medical therapy.

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